International Ibuprofen Foundation

Written submission to the NDAC meeting

on risks of NSAIDs

presented by the

INTERNATIONAL IBUPROFEN FOUNDATION

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Non-prescription use of ibuprofen and the risks of gastrointestinal and renal toxicity

1. Introduction

The purpose of this briefing document is to provide information about the safety and efficacy of ibuprofen for non-prescription use, and to distinguish the safety of non-prescription use from the adverse events associated with prescription use.

2. The International Ibuprofen Foundation

The International Ibuprofen Foundation (IIF) aims to assist and collaborate with the FDA and other global regulatory agencies to find better ways to communicate information to the consumer and make over-the-counter medications safer for consumer use.

IIF was set up by a group of companies with international interests in the marketing of analgesic products based on ibuprofen, with particular reference to self-medication. Its purpose is to act as a central source of technical and medical data on the use of ibuprofen and its widespread value as a potent, effective and safe analgesic for general use. This includes advice and assistance over media enquiries, technical information backup, and access to reliable and accurate medical information and opinion on ibuprofen issues both technically and commercially. IIF has developed a website to help educate consumers and health professionals about ibuprofen (www.ibuprofen-foundation.com).

The Foundation also develops position papers on major topics relating to ibuprofen, seeks medical help and advice in this respect and organises meetings, workshops, seminars or conferences. In April 2002, IIF supported an international symposium at the Royal College of Physicians, London, *Ibuprofen Through the Ages: Past, Present*

and Future, chaired by Professor Sir John Vane (highlights and full proceedings of this meeting are in press).

3. Prescription and non-prescription doses of ibuprofen

The development and introduction of ibuprofen has been described by Rainsford (1999a). Ibuprofen was the product of a research programme specifically to develop a well tolerated drug for the treatment of inflammatory arthritis. It was first introduced in the UK in 1969 as a prescription-only medicine for the treatment of rheumatoid arthritis; the licensed dose of 600 - 800 mg was increased to 1200 - 2400 mg/day as clinical experience of efficacy and safety accumulated. When ibuprofen was introduced in the United States in 1974, the licensed dose was 1200 - 3200 mg/day. Ibuprofen became available without prescription for the treatment of acute minor pain in the UK in 1983 and in the United States in 1984; the licensed dose was 1200 - 1600 mg/day.

4. Mechanism of action

Ibuprofen is a non-selective inhibitor of cyclo-oxygenase (COX) 1 and 2. It has analgesic, antipyretic and anti-inflammatory activity (Rainsford, 1999b).

5. Risk of gastrointestinal toxicity of NSAIDs

Ibuprofen is associated with the lowest risk of gastrointestinal complications of any NSAID at prescribed doses (Henry et al, 1996; Doyle et al, 1999; Henry and McGettigan, 2002). In the doses used for self treatment, the incidence of gastrointestinal events in adults is low (Moore et al, 1999; Kellstein et al, 1999) and in children is low and comparable with that associated with acetaminophen (Lesko and Mitchell, 1999).

5.1 Ibuprofen compared with other NSAIDs

The relative risk of gastrointestinal complications associated with NSAIDs has been estimated in a meta-analysis of 12 case-control and cohort studies of the risk of admission for peptic ulcer complications associated with NSAIDs (Henry et al, 1996). Ibuprofen was associated with the least risk of serious upper gastrointestinal complications; by comparison, the unadjusted risk was 1.6 (fenoprofen) - 9.2 (azapropazone) times greater with other NSAIDs.

This meta-analysis further explored the effect of dose on risk using definitions of low and high dose defined in the original publications. These studies variously defined low-dose as less than 1200, 1500 or 2400 mg/day. The relative risk for low-dose ibuprofen was 1.6 ($CI_{95\%}$ 0.8 - 3.2) and for high-dose ibuprofen it was 4.2 ($CI_{95\%}$ 1.8 - 9.8).

A recent update of this meta-analysis included data published up to June 2001 (Henry and McGettigan, 2002). 36 case control studies and 8 controlled cohort studies now met the eligibility criteria. The case control studies involved 19,648 cases and 105,373 controls; the cohort studies involved approximately 400,000 exposed subjects and 1 million non-exposed controls. This analysis found that, compared with non-use of NSAIDs, the adjusted relative risk of serious peptic ulcer complications was 2.22 for ibuprofen ($CI_{95\%}$ 1.7 - 2.29) and ranged from 3.13 for aspirin ($CI_{95\%}$ 2.4 - 4.1) to 8.7 for piroxicam ($CI_{95\%}$ 6.2 - 10.4). This analysis of prescription use of NSAIDs also confirmed the reduced risk at lower doses of ibuprofen.

5.2 Risk of gastrointestinal toxicity with non-prescription ibuprofen

The risk of adverse events associated with multiple-dose use of non-prescription ibuprofen has been evaluated in a meta-analysis of eight placebo-controlled studies in (Kellstein et al, 1999). The doses ranged from

800 to 1200 mg/day; the duration of use ranged from 1 to 10 days. The frequency of adverse gastrointestinal events was 12.1% with ibuprofen and 11.0% with placebo (p=0.420). The overall frequency of adverse events was significantly greater with placebo than with ibuprofen (31.7 vs. 27.4%, p=0.018).

In a prospective study of ibuprofen use in healthy volunteers taking the maximum permitted non-prescription dose of ibuprofen (1200 mg/day for 10 days), there was no significant difference in the incidence of adverse gastrointestinal events (placebo 16%, ibuprofen 19%; p=0.187) or in the proportion of subjects who had positive occult blood tests or who withdrew from the study due to such events (Doyle et al, 1999).

Adverse events associated with non-prescription use of ibuprofen were evaluated in the PAIN (Acetaminophen, Aspirin, Ibuprofen New tolerability) study (Moore et al, 1999). This blinded randomised parallel-group comparison of the tolerability of over-the-counter analgesics in the treatment of common types of acute pain involved 8677 adults aged 18 - 75. Treatment comprised ibuprofen 1200 mg/day, acetaminophen 3 g/day or aspirin 3 g/day for 1 - 7 days. Exclusion criteria were principally the contraindications to treatment with any of the drugs. The primary endpoint was the number of patients with at least one significant adverse event.

The incidence of adverse events is summarised in Table 1. Significant adverse events were reported by 18.7% of patients taking aspirin, 13.7% of those taking ibuprofen and by 14.6% of those taking acetaminophen (p<0.001 for aspirin vs. ibuprofen). Significant gastrointestinal events were less frequent with ibuprofen (4.0%) than with aspirin (7.1%, p<0.001) or

acetaminophen (5.3%) (p=0.025), in particular dyspepsia (1.4% vs. 3.1% with aspirin, p<0.001; and 2.2% with acetaminophen, p<0.019), abdominal pain (2.8% vs. 6.8% with aspirin, p<0.001; and 3.9% with acetaminophen, p<0.24); nausea was more frequent with aspirin (2.5%) than ibuprofen (p=0.01) or acetaminophen (1.5% each). There were no significant differences between the treatments in events associated with other organ systems. Subgroup analysis showed that the risk of adverse effects was not significantly different by age, sex and indication.

A randomised community-based study in febrile children aged 2 years old compared the safety of ibuprofen (5 or 10 mg/kg) and acetaminophen (12 mg/kg) (Lesko and Mitchell, 1999). The risk of hospitalisation for gastrointestinal bleeding associated with ibuprofen was 17 per 100,000 ($CI_{95\%}$ 3.5 - 49); this was not significantly different from that with acetaminophen. The risk of hospitalisation for vomiting or gastritis was also similar.

6. Renal effects

Renal adverse events associated with NSAIDs are uncommon at prescribed doses but may be severe. Short half-life NSAIDs such as ibuprofen are associated with a lower risk of renal effects than NSAIDs with a longer half-life (Stürmer et al, 2001). Short-term use of ibuprofen does not significantly increase the risk of renal impairment in healthy volunteers (Murray and Brater, 1999; Svendsen et al, 2000) or in children with febrile illness (Lesko and Mitchell, 1997; Lesko and Mitchell, 1999). Long-term treatment with ibuprofen at a dose of 1200 mg/day does not increase the risk of renal impairment in elderly people (Griffin et al, 2000). Ibuprofen is associated with a low risk of renal toxicity in overdose (Jenkinson et al, 1988; Volans and Fitzpatrick, 1999).

6.1 Healthy individuals

Short-term use of therapeutic doses of ibuprofen poses little risk of adverse renal effects in healthy individuals (Murray and Brater, 1999). In a placebo-controlled study in healthy adult volunteers, ibuprofen 800 mg twice daily for 14 days did not alter renal haemodynamics, net excretion of electrolytes or urinary excretion of albumin; ibuprofen was associated with a decrease in plasma renin concentration (Svendsen et al, 2000).

6.2 Febrile children

Renal function was monitored in a subgroup of children (285 of 27 065) who were admitted to hospital while participating in a randomised double-blind trial of 5 or 10 mg/kg of ibuprofen or acetaminophen 12 mg/kg for the treatment of febrile illness (Lesko and Mitchell, 1997). There was no difference between the treatments in blood urea nitrogen levels, serum creatinine concentrations or the incidence of serum creatinine concentrations > 62 micromol/l. The authors concluded these data suggest that the short-term risk of less severe renal impairment associated with short-term use of ibuprofen in children is small and not significantly different from that with acetaminophen. There was also no difference between ibuprofen and acetaminophen in the risk of admission for acute renal failure (Lesko and Mitchell, 1999).

6.3 Elderly people

A case-control study in 1799 elderly (> 65 years) patients with community-acquired renal failure found that 18.1% were taking prescribed NSAIDs compared with 11.3% of controls (Griffin et al, 2000). After adjustment for demographic factors and comorbidity, prescribed NSAIDs were associated with an increased risk of renal failure in this population (odds ratio 1.58; $CI_{95\%}$ 1.34 - 1.86). The odds ratio for ibuprofen at doses of 1200 mg/day was 0.94

($CI_{95\%}$ 0.58 - 1.51); larger doses of ibuprofen were associated with higher odds ratios (>1200 - 2400 mg/day: 1.89, $CI_{95\%}$ 1.34 - 2.67); >2400 mg/day: 2.32, $CI_{95\%}$ 1.45 - 3.71).

6.4 Chronic use

An analysis of risk factors in 802 patients treated with NSAIDs for osteoarthritis found a marginal increase in the risk of renal impairment (odds ratio 1.4, $CI_{95\%}$ 0.9 - 2.2); this was almost exclusively attributable to agents with a half-life of 4 hours or greater (OR 2.6. $CI_{95\%}$ 1.2 - 5.7) (Stürmer et al, 2001). NSAID use did not significantly increase the risk of renal impairment in patients taking diuretics or ACE inhibitors. The elimination half-life of ibuprofen is approximately 2 hours and this is not significantly increased in elderly people (Brocks and Jamali, 1999).

6.5 Overdose

Although impairment of renal function following NSAID overdose would be predicted, reports of renal effects are infrequent in practice. The renal effects of ibuprofen are dose-related, with clinical effects more likely at blood ibuprofen concentrations greater than 280 mg/l (Jenkinson et al, 1988). It is likely that lower doses produce minor changes in renal function which are not usually detected unless more sensitive tests are used. From the clinical viewpoint this is probably of no importance (Volans and Fitzpatrick, 1999).

Where renal failure has been reported, there has usually been a massive overdose of ibuprofen with consequent metabolic acidosis and oliguric renal failure. It is likely that the acidic metabolites play a major part in this presentation and there are well described cases where patients have recovered following short-term treatment with haemodialysis. In other cases,

renal failure appears to related to additional factors such as pre-existing renal disease, serious infection, binge drinking or dehydration (Volans and Fitzpatrick, 1999).

7. Conclusions

Based on the comprehensive review and analyses of available data, although ibuprofen is the safest of the NSAIDs there appears to be a dose-related risk for GI and renal adverse events. However, at OTC doses of 1200 mg/day or less, the risks appear negligible and there is a relatively wide therapeutic window to the commonly used prescription doses of 2400 - 3200mg/day. The key to further minimizing risks to the consumer is to continue to find better ways to encourage consumers to read, comprehend and comply with the current label warnings and directions. The IIF hopes to work closely with global regulatory bodies to communicate these public health issues to the consumer.

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Table 1. Frequency of adverse events in the PAIN study (% patients affected)

Adverse events*	Aspirin	Ibuprofen	Acetamino-phen	Ibuprofen vs. aspirin	Ibuprofen vs. acetamino-phen
All significant events (ITT)	18.7	13.7	14.6	p<0.001	NS**
Severe events	4.8	3.5	3.2	p=0.014	NS
Moderate events	12.2	8.5	10.2	p<0.001	p<0.02
Events leading to premature discontinuation	7.6	8.1	6.1	p<0.001	NS
Events leading to additional consultation	4.9	3.5	3.5	p=0.009	NS

** not statistically significant (p>0.05)